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Review article

Lung cancer from passive smoking: hypothesis or convincing evidence?

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Summary. The epidemiological literature on passive smoking and lung cancer is reviewed and the well-known criteria for establishing a causal relationship are applied in order to determine what level of causal evidence currently exists. Three cohort studies and 12 case control studies are analysed. Of the prospective cohort studies, one contributes very little to our knowledge, one shows no risk increase and one results in a moderate risk increase of 1.74 for women married to heavy smokers. The last is the only study which has to be taken seriously, even when other considerations show that its results might be caused by chance, bias or confounding. None of the six case control studies yielding a positive relationship was conducted according to the state of art of epidemiological research, giving reasonable and sound evidence which cannot be explained by chance, bias, confounding or misclassification. Two studies contribute nothing to the evidence. None of the four case control studies yielding no risk change or a risk decrease can exclude the possibility that a causal relation exists. The epidemiological and toxicological evidence is discussed in the light of recent findings. The volume of accumulated data is conflicting and inconclusive. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk. Applying the criteria proposed by IARC there is a state of inadequate evidence. The available studies, while showing some evidence of association, do not exclude chance, bias or confounding. They provide, however, a serious hypothesis. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

Key words: Passive smoking – Lung cancer – Causal connection

Introduction

Active smoking is the most important, avoidable health hazard in industrialized countries. If passive smoking causes lung cancer, this would be a very strong argument against active smoking. It could be the decisive argument for reducing active smoking considerably. Science should determine whether this hypothesis is true or not. If it is to do so, one must seek to state the facts and to separate these from mere speculation.

There are eight well established criteria which should be fulfilled if a causal connection in epidemiology is to be inferred:

- *Consistency* of the association in various studies. The results should be reproducible in similar circumstances.
- *Strength and intensity* of the association. Risk ratios of 5, 10 or greater are more likely to indicate a causal relationship than a risk ratio of around 2.
- *Specificity* of the association. The exposure, the effect and the way in which the exposure works should be specific. Therefore exposure and effects should be measured with sufficient validity and specificity.
- There should be a *dose-response relationship*.
- *Exclusion of bias and confounding factors*.
- There should be *statistical significance*.
- *Impact of intervention*, i.e. there should be studies showing a decrease of the effect when the exposition has been diminished.
- There should be *biological plausibility*.

Taking these criteria into consideration, the IARC has proposed four different levels of evidence [22] when evaluating the existence of a causal relationship regarding carcinogenicity in humans:

(1) Sufficient evidence of carcinogenicity: There is a causal relationship between the exposure and human cancer.
(2) Limited evidence of carcinogenicity: A causal interpretation is credible, however, alternative explanations (such as chance, bias, confounding) cannot adequately be excluded.
(3) Inadequate evidence: There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
(4) No evidence: Several adequate studies are available which do not show evidence of carcinogenicity.

In this article the available literature is examined in light of the criteria required to infer a causal connection and thus to determine what IARC level of causal evidence currently exists.

Cohort studies

Adequate and well conducted cohort studies can provide sound, empirical evidence on a causal relationship between exposure and event. To date, three cohort studies on passive smoking (from Hirayama, Garfinkel and Gillis et al.) have been published.

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Evidence from this study has been published in four reports [18, 19, 20, 21]. In addition there are several critical comments [4, 24, 32, 33, 34, 37, 38, 47, 48, 49, 54, 60]. Married, nonsmoking women aged 40 and above (n = 91540) from a cohort of 265118 adults in 29 health center districts in Japan were followed for 15 years. Altogether, 200 women died of lung cancer. Standardized mortality rates for lung cancer were calculated according to the smoking habits of the husbands. The point estimate of the rate ratio was 1.74 or 1.79 when comparing women of nonsmoking husbands to women whose husbands smoked more than 20 cigarettes per day. There was a dose-response relationship which was also significant. Standardization using the age of women and the occupation of husbands was performed. In nonsmoking men with smoking wives, seven lung cancer deaths occurred, resulting also in a relative risk of around 2.

In evaluating the results of this study the following points must be taken in consideration:

(1) The study was designed to screen for a wide variety of possible risk factors on life events and not to test the hypothesis that passive smoking causes lung cancer. It therefore cannot prove this hypothesis, but rather can only generate it. The hypothesis that passive smoking causes lung cancer is one of several secondary hypotheses which can be extracted from this material.

(2) The reported cohort is not representative of the population of Japan. The age distribution of females over 40 in Japan in 1965 was different from the age distribution in the cohort [44]. Of 265118 adults (122261 men and 142857 women) only 91540 nonsmoking married women, whose husbands smoking habits were known, were included in the study. 51317 women (35.9%) were not used, partly because the smoking habits of the husbands were not known and the corresponding 103 nonsmoking lung cancer cases were not entered in the study. Even when most of them were not married, some selection mechanism was at work. The precise effect of this selection, for instance, regarding occupation of wives, is unpublished and unknown.

(3) The indicator, by which the exposure to passive smoking was estimated, was neither specific nor was its reliability or validity assessed [24]. The state for a woman "being a nonsmoker and being married to a man who smokes a certain number of cigarettes" was registered once in 1965. The duration of this status is unknown and was not accounted for. A woman living with a smoker in 1965 for a year and then dying of lung cancer was treated as married to a smoker in the same way as a woman being a passive smoker for 30 years. A woman, who began smoking a year after the start of the study and who died of lung cancer, was treated as a nonsmoker. The exposure to sidestream smoke in the working place for women – approximately 45% for men and 25% for women of the total exposure in Germany [40] – is not contained in the indicator. Being married to a man who smokes might mean a lot of other risks influencing the cause of death, for instance risks from food, environment, social conditions, living in cities or in villages, size of living space at home, or occupation of the women. The selection of partners will most certainly introduce some other risk factors which have not been

accounted for. It has been shown that being married to a man who smokes is consistent with a wide variety of exposure to sidestream smoke [11, 39, 59]. One study [11] shows, that 40 to 50% of persons with nonsmoking spouses reported some passive exposure and conversely 30 to 35% who were married to smokers reported no exposure. The concordance on directly and indirectly reported smoking habits of the spouse was 85% in another study [36]. Being married to a man who smokes is not a valid and accurate indicator of the extent to which one is exposed to passive smoking and is by no means specific.

(4) The event – dying from lung cancer – was not assessed in a way which corresponds to the state of the art. It is well known that the causes of death on death certificates disagree to a certain extent with the real cause of death. It is safe to assume that at least 10% have died from causes other than those specified on the death certificate. In one study [13], the cause of death on death certificates was not confirmed by the treating physician in 16.7% of the lung cancer cases. An autopsy was available from only 23 (11.5%) of the 200 cases. However, the histological type of lung cancer is decisive in establishing a causal connection. Women frequently have adenocarcinomas, a histological diagnosis that is not believed to be connected to smoking as strongly as squamous or small cell carcinoma. Neither the exposure nor the event were assessed or monitored in a way approaching the standards which are applied in other fields of risk evaluation, for instance in studies on adverse drug reactions.

(5) Various confounding factors were not adequately considered in this study; for instance, exposure to other substances in the working place, (dust, fumes or vapours), overall air pollution, exposure to indoor pollution, such as kerosene stoves, genetic condition, food, type of medical care and others.

(6) Bias in registering the fact that a woman was a nonsmoker, was neither controlled for nor excluded. Some women who were active smokers might have declared themselves nonsmokers in a society where smoking women were not well accepted and who made up an absolute minority. Such women developing lung cancer will then be included as cases.

(7) The percentage of possible misclassifications and its likely effect on the results have not been examined. With a certain percentage of misclassifications in the category "nonsmoking women" among the lung cancer cases, the statistical differences will disappear. Recent studies [26, 35] have shown that misclassification can easily explain the association between lung cancer and passive smoking in case control studies.

(8) Almost nothing was reported on the 200 cases. There are no case reports available, from which individual histories can be judged or at least partly evaluated regarding other relevant factors. This is standard in other areas, e.g. the evaluation of rare adverse side effects from drugs. The core of evidence we have on the cases is that, during 1965, 200 women in Japan told an interviewer on a single occasion that they were, at that time, nonsmokers, married to a smoker and their death certificate subsequently contained

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the (perhaps erroneous) diagnosis lung cancer. This information is not very convincing to a scientist.

(9) The trend in lung cancer rates in Japan between 1950 and 1979 was over nine-fold in men and over six-fold in women [31]. This risk increase cannot be explained by passive smoking. Comparing the total population to that of nonsmokers from Hirayama's own data, this ratio is only four-fold in men and just under two-fold in women. This indicates that there might be some other important cause of lung cancer which was not studied.

(10) Some statistical arguments have to be kept in mind: Nobody knows how many tests have been applied to this material. Adjustments for multiple tests, however, would considerably reduce significance levels. Statistical tests with huge numbers in the denominator are not as convincing as the accompanying small type I error indicates. The larger the number and the smaller the incidence, the more important are bias and confounding. For very small incidences, the theoretical models are not very appropriate. Diamond and Forrester [10], using a Bayesian approach, have shown how small the posterior probability for Hirayama's hypothesis could be. Using their analysis, Hirayama's results could well be consistent with the null hypothesis. The statistical significance of Hirayama's risk ratios could be a matter of chance or an artifact induced by some of the many problems occurring in such a large study.

Considering all these arguments, the study at best suggests the hypothesis of a causal association. Still, the null hypothesis might also be true. Even when a dose-response relationship seems to exist in this study, chance, bias or confounding factors could as adequately explain the results as does the hypothesis that passive smoking causes lung cancer.

Garfinkel

This re-analysis [13] uses data from the ACS-study [12] and from the Dorn study [57] in the USA. Nonsmoking women (n = 176, 739) married to men with known smoking habits were included. The period from 1955–1972 was covered. The relative risk adjusted for several factors was 1.04 when women married to nonsmokers were compared to women married to husbands smoking more than 20 cigarettes per day. There was no statistical significance and no dose-response relationship. The authors argue that if passive smoking is of practical importance, then there should be an increase in death rates due to lung cancer among nonsmokers. This could not be found.

The sample size and the level of details of this study are comparable to Hirayama's material. Some information, for instance on histology, is more specific. There is, however, no indication of a statistical connection between passive smoking and lung cancer. The paper failed to reproduce the Hirayama results and did not add evidence to this hypothesis. If there is a relevant increase in lung cancer risk from passive smoking, it should also have shown up in Garfinkel's study. The Garfinkel study does not of course disprove the Hirayama hypothesis.

Gillis et al.

This study was published in 1984 [15] and presents only very few cases (6 men and 8 women) with lung cancer among nonsmokers. It does not show any trend or statistical significance because of these small numbers. This study contributes very little to the empirical evidence in either direction.

Summarizing the evidence from cohort studies, the conclusion is that only the Hirayama study, which has severe drawbacks, provides any empirical evidence in favour of the hypothesis that passive smoking may cause lung cancer in nonsmokers.

Case-control studies

In assessing the relative risk of rare events, case control studies can provide valuable information by estimating odds ratios. Such studies cannot prove a causal connection. They can, however, give sound empirical evidence, provided several studies have consistently similar results, the effect and the event are determined with some validity, the odds ratios are large and bias can be adequately excluded. Twelve case-control studies have been published so far on the relationship between passive smoking and lung cancer.

Trichopoulos et al.

In this study [55, 56], 77 nonsmoking women with lung cancer and 225 nonsmoking women with other diseases were compared with regard to the smoking habits of their husbands. The authors calculated an odds ratio of 2.4 and 3.4 when comparing women married to nonsmokers with women married to men who smoke less than one pack of cigarettes per day and more than one pack per day respectively. The linear trend of these ratios is significant. The authors were aware of some of the limitations of this study and concluded that further investigations were warranted.

The Trichopoulos study is a textbook example for some of the errors which must be avoided if a case-control study is to be valid:

- The cases are from three cancer hospitals, the controls from a hospital for orthopedic disorders. A systematic bias is therefore likely.
- An interviewer bias must be expected: the same medical doctor selected the controls and interviewed them. He was fully aware of the goal of the study.
- A bias in recalling the passive smoking history is likely in patients. At least some of the cases knew their diagnosis, whereas the controls were not aware of a life-threatening disease.
- Patients with adenocarcinoma and with alveolar carcinoma were excluded, so that there was a selection among the lung cancer cases. This makes it a study of a subset of lung cancer more associated with active smoking.
- The histological type of lung cancer is not available in 35% of the cases.
- In assessing the exposure, there is no specificity and no validity. Misclassification might have occurred [26, 35]. Being married to a cigarette smoker

may not be a valid indicator of exposure to passive smoking and could indicate various other risks.

- Confounding factors, such as exposure at the work place, food, etc. were not considered.
- The calculated odds ratios are incorrect, they should be 1.95 and 2.54 [16].
- The risk of active smoking is on the same size order as that of passive smoking, a result that is biologically implausible.

The total number of cases is small. The statistically "significant" results of this study might well be artifacts from chance, bias or confounding. The study provides no valid evidence for a causal connection of passive smoking and lung cancer.

Correa et al.

Lung cancer patients ($n = 1338$) from a large number of hospitals in Louisiana were compared to 1393 controls from the same hospitals with regard to the smoking habits of spouses and parents [7, 8]. Eight male nonsmokers (from 1036) and 22 women nonsmokers (from 302) could be used for calculating odds ratios with regard to passive smoking.

The exposure was estimated in total lifetime pack-years by interviewing patients or their next of kin. Women married to smokers with more than 40 pack-years had an odds ratio of 3.52, which was significant ($P \leq 0.05$). Various other odds ratios were calculated but were within chance limits. The authors concluded that the similarity of their findings with those of Trichopoulos strengthened the suspicion that passive smoking may contribute to lung cancer. The study also revealed a relative risk of 1.66 for patients whose mothers smoked and of 1.04 if the father was a smoker. The relative risk for patients whose mother smoked decreased to 1.36 when one takes into account the active smoking of the subject. The effect of maternal smoking is only significant in males. How maternal smoking causes lung cancer in males, but not in females, can only be a matter of speculation according to the authors.

The numbers of nonsmoking cases are small. Misclassification could be a sufficient explanation for the association. In view of the many calculated odds ratios, one single ratio reaching $P \leq 0.05$ is not surprising. There might be a selection bias. 76% of the cases and 89% of the controls were interviewed by professional interviewers. It was not mentioned which percentage of the patients themselves and which percentage of the next of kin gave the information. This might be different in cases and controls. The inconsistencies in this publication can most easily be explained by the large number of odds ratios calculated from very few nonsmoking cases, by possible bias, by chance, or by confounding factors. The study does not provide convincing evidence for a causal relation between passive smoking and lung cancer.

Sandler et al.

The authors published three reports from the same data base [50, 51, 52], covering in the first paper the effect of smoking of the spouse, in the second

paper the combined effect of father, mother and spouse, and in the third paper only the childhood exposure. Several critical comments have been published [5, 17]. Cancer cases from all sites ($n = 518$) were compared to 518 controls in the first paper, and an odds ratio of 1.6 for all cancer sites and one of 1.6 for lung cancer was reported.

These results are not very meaningful for a variety of reasons. Controls were selected by cases in 60%. The cases answered questions on smoking, knowing that they had cancer and that there is a relation between smoking and cancer. They proposed friends without cancer to answer questions on smoking, thereby possibly selecting friends with less exposure to smoke. The level of education differs significantly between cases and controls together with other confounding variables connected with education. The reporting was not comparable between cases and controls: the number of missing values on marital status and occupation are different and the same might have been the case in reporting on passive smoking. The results are not presented by age and sex of the nonsmokers, so that details of the calculations cannot be verified. Combining all types of cancer with different etiology and epidemiology does not make biological sense. The crude odds ratio for smoking is much smaller than the one for passive smoking, which is biologically implausible. The authors claim that passive smoking is related to a number of cancers not related to active smoking, which is not plausible, because active smokers are more exposed to sidestream smoke than nonsmokers. There was no clearcut dose-response relationship. Exposure outside the home was disregarded. Misclassification could explain part or all of the results. The evidence for lung cancer is especially weak: there were only 22 cases reported, 20 of them smokers, so that the whole evidence on passive smoking and lung cancer in this study is based on two nonsmoking lung cancer cases.

In the second and third papers, there is no further serious evidence on lung cancer caused by passive smoking. A large number of odds ratios and error probabilities is calculated, based essentially on the same two nonsmoking cases as in the first paper. Adjusting for multiple factors can add nothing to the evidence in such a case. There are at best hypotheses generated, most of which will not be reproducible in further studies.

Chan and Fung

In this paper [6], 84 female nonsmoking lung cancer patients were compared to 139 controls regarding the smoking habits of spouses. The authors gave the numbers, but did not calculate the odds ratio, which is 0.75 and within chance limits. This study – giving the histological type of tumor and some information on cooking habits – does not support the hypothesis that passive smoking causes lung cancer.

Koo et al.

Koo et al. have presented three papers on the subject [28, 29, 30], giving an analysis of risk factors in 1781 lung cancer cases from Hongkong in the first. Since it is not evident from the second and third papers whether they refer at

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least partially to the same cases, only the second paper with 200 cases and 200 controls is considered here. The third paper with 120 cases and 120 controls had very similar results.

Two hundred female lung cancer cases were compared with 200 female controls regarding the exposure to passive smoking. Eighty-eight cases and 137 controls had never smoked (66 and 97 with passive smoke exposure, odds ratio 1.24) and 112 cases and 63 controls had smoked. The histological diagnosis is provided for all cases. A very detailed interview of all cases and controls was conducted by trained interviewers. The information on the patients and controls is more detailed than in all other studies. The exposure to sidestream smoke at home and at work was included in the analysis and an attempt was made to quantify exposure. The calculated odds ratio is not significant. There was no dose-response relationship. The original 200 cases and controls were age-matched. However, these who had never smoked could have had another age distribution and no age standardisation was carried out. This study does not support the hypothesis that passive smoking causes lung cancer.

Kabat and Wynder

The authors [25] compared 134 nonsmokers out of 2668 lung cancer patients with 134 nonsmoking controls, which were age-, race- and hospital-matched. The groups were comparable regarding religion, proportion of foreign born, marital status, residence, alcohol consumption and Quetelets index. Male cases tended to have higher proportions of professionals and to be more highly educated than controls. No difference in occupation or occupational exposure was seen in men. The histological type of lung cancer in lifelong nonsmokers and in smokers was described for 882 men and 652 women. Information on passive smoking was available in 25 male cases and controls and in 53 female cases and controls. Spouses' current or past smoking habits were known in 36 cases and controls. There was no increase in risk comparing exposure at home or at work in women, and in men at home. Only in the subgroup of men with exposure at work was there a risk increase for the cases, the difference being just significant ($P \leq 0.05$). Such subgroup analyses are however misleading. Overall this study does not support the hypothesis that passive smoking causes lung cancer.

Miller

In this paper [43] information was gathered (telephone interviews with the next of kin) from 1838 cases out of 4130 deaths in Pennsylvania during 1975 and 1976. Nonsmoking women ($n = 537$), who were married and of whom there was information on the smoking habits of the husband, were analysed.

Odds ratios were calculated for various subgroups comparing all cancer deaths with all deaths by other causes regarding the smoking habit of the husband. The author concluded that the results of the study provide support for the hypothesis that long-term passive smoking leads to excess cancer deathrates in

exposed nonsmokers. The data simply do not support such an hypothesis. In particular:

- 44% of the available deaths were omitted because of incomplete information.
- If the correct formulas are applied to the data and if age standardization is performed, the odds ratios are well within chance limits.
- Confounding factors and bias in reporting are not seriously considered.

This study, since it was not performed according to the state of the art, adds nothing to our knowledge.

Garfinkel et al.

In this case-control study [14] the authors compare 134 carefully selected nonsmoking women with lung cancer to 402 controls with cancer of the colon/rectum. The cases were selected from hospital records and special attention was given to a verified histological diagnosis. The exposure to passive smoking was assessed by a standard interview and a quantification of the exposure was attempted. The overall result was – considering the total exposure at home and at the working place – that there is no significant risk increase. The odds ratio was 1.28 for the exposure during the last five years and 1.12 for the last 25 years. There was no dose-response relationship regarding the overall exposure. Analysing various subgroups, there was one subgroup with a marginally significant risk increase: women married to men smoking more than 20 cigarettes per day at home (OR = 2.11, $P \leq 0.05$). There is no evidence of a passive smoking relationship where the data come from the woman or her husband. The odds ratios (OR) increased if the exposure history was not taken from the patient herself or from her spouse, but rather from other relatives or friends. A logistical regression analysis, adjusting for age, hospital, socio-economic status and year of diagnosis, arrived at approximately the same type I error rate.

This meagre result is weakened by the following considerations:

- A bias due to misclassification of active smoking might exist. The smoking habit was assessed in more than half of the cases not by themselves or by their husbands, but rather by their children or someone else. This was done several years after the diagnosis, in many cases several years after death, and the relevant information had to include the time 20 and more years before. Active smoking of some cases that long ago might not have been known to the person interviewed.
- There is no evidence of an association when the data on smoking habits came from the woman themselves or from their husbands; it only appeared when the daughter, son or another person supplied the information.
- A lot of odds ratios were calculated in subgroups, which were not independent. If one adjusted for multiple testing, none of the slightly significant numbers would remain significant. The analysis of subgroups using confidence intervals quite often leads to invalid results and in this study also the negative fluctuations around the chance level have to be considered.
- The study presents direct evidence that misclassification of the subject smoking habits can bias estimates of passive smoking upwards. A strong associa-

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– The high percentage of adenocarcinomas which are less typical of active smoking could explain the meagre result of this study.

The study does not provide evidence to support the hypothesis that passive smoking causes lung cancer.

Lee et al.

In the latter part of a large hospital case-control study [36] of 56 lifelong, non-smoking lung cancer cases who were married once, 34 spouses were successfully interviewed on their cigarette consumption. A wide range of potential confounding factors was considered. The spouses of 80 matched controls, whose condition was not related to smoking, were interviewed in the same way. Various odds ratios were calculated. Passive smoking was not associated with any significant increase in risk of lung cancer amongst lifelong nonsmokers. The overall relative risk was 0.80 with an upper confidence limit of 1.50, which is less than some of the larger increases claimed in other studies. The authors discussed limitations of past studies and concluded that any risk increase by passive smoking is at most small and may not exist at all.

The number of cases in this study is small and the type II error is therefore large. The study does not contribute positive evidence to the hypothesis that passive smoking causes lung cancer, nor does it disprove it.

Akiba et al.

Lung cancer cases and controls from Hiroshima and Nagasaki atomic bomb survivors were compared in this study [1]. There were 113 nonsmoking lung cancer cases, 94 of them women. Various odds ratios were calculated. The authors reported an overall odds ratio of 1.5 for lung cancer among nonsmoking women whose husbands smoked, which was just not significant at conventional levels. The risk tended to increase with amount smoked by the husband and to decrease with cessation of exposure.

Most of the cases had died before the study was conducted. In only about 10% of the cases could the smoking habits of the husband and other information be obtained directly from the cases. Only 52% of the cases were verified by autopsy. There is some possibility of bias in this study left: a fact that led the authors to conclude that further studies were warranted where passive smoking exposure could be more fully quantified.

Dalager et al.

The authors [9] combined the cases from three case-control studies which had been published earlier [3, 7, 62]. Ninety-nine nonsmoking, histologically confirmed lung cancer cases were compared to 736 controls. The cooperation rate, the source of passive smoking data, the gender groups included, the racial

groups included and the study design varied between Louisiana, Texas and New Jersey. The original studies had opposite outcomes, Louisiana showing a positive relationship, and Texas a negative one. Only the home exposure to passive smoking was considered. There was no increase in the risk of lung cancer controlling for gender, age and study area as confounders (OR = 0.84). Searching in subgroups, several analyses were performed leading to an odds ratio of 1.47 (only Louisiana and New Jersey, only smoking pattern of spouse), which was not significant. A dose-response relationship occurred only among females with increasing pack-years of exposure to spouse smoking, with an OR = 2.99 for females with more than 35 pack-years of exposure. Here studies were not combined, and only Correa's Louisiana data were reiterated. Considering histological types, the adjusted odds ratios were also not significant. The highest OR = 2.88 was found for squamous and small cell carcinoma.

Most of the calculated odds ratios do not approach significance levels. The same sources of bias are existent here as in the study from Correa. Subgroup analyses have no confirmatory value. There was no adjustment for multiple testing. Misclassification might be present. The study does show that the same type of bias could be present in all three case control studies. Especially in older females, whose husbands are heavy smokers, bias might be more important. Any effect seen was limited to one of the three states, was of marginal significance and of doubtful validity. This study, combining data from three sources and searching in subgroups, does not contribute convincing evidence for the hypothesis that passive smoking causes lung cancer.

Knoth et al.

This study [27] is not a case-control study in the strict sense. The authors found that from 39 female nonsmoking lung cancer cases, 24 (61.5%) were married to a smoking husband or were living together with a smoker. They compared this percentage with the percentage of smoking men 50 to 69 years of age in the population, which was, according to their sources, nearly three times smaller (22.4%). They felt that passive smoking was the most likely explanation. In comparing these two percentages, other explanations are at least equally likely.

The real percentage of female nonsmoking lung cancer cases married to smoking males might be smaller than the one calculated from the study group. The smoking habit was known only for approximately 35% of the original group, making selection bias and interview bias a distinct possibility. More answers can be expected from couples with a smoking husband. The duration of smoking and the time of exposure was not clearly specified, nonsmoking men who had been smokers were also included. The percentage of female lung cancer cases married to cigarette smokers is not a valid indicator of exposure.

On the other hand, the percentage to be expected in such a group was not estimated properly. Around 38.6% of the men were active smokers in the "microcensus" conducted by the Federal Office of Statistics in 1980. In this census the definition of smoking is different from the one used in the study group. The selected age of 50 to 69 years is not well matched to the age of men in the study group and 22.4% was the average percentage of both male and

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female smokers. 58% of all men and women in Germany are smokers at some time during their life [40] and of these 36.7% are smokers. The percentage of men who smoked sometime during their life is higher than 58% in the older age groups in men, most likely around two thirds of the population. It is therefore not unexpected that 61.5% of female lung cancer cases were married to such men.

Comparing two improperly estimated percentages is not an acceptable method for epidemiological reasoning. This study adds nothing to the evidence that passive smoking might cause lung cancer.

Epidemiological evidence

To date, there have been no animal studies published in which lung cancer is produced by applying sidestream smoke. Evidence on a causal relationship between passive smoking and lung cancer can therefore only be based on epidemiological studies in man.

Of the three prospective studies, only one [18, 20] shows a moderate risk increase of 1.74. This study by Hirayama cannot be regarded as really indicative, because it might be seriously flawed. It is, however, the only study which, since it does give some empirically sound evidence, should be taken seriously.

Of the 12 case-control studies, two [27, 43] contribute nothing to the evidence, six show a moderate risk increase [1, 8, 9, 14, 50, 56], but do not sufficiently exclude chance, bias and confounding, four studies [6, 25, 29, 36] show a moderate risk decrease or no risk change. The histological type of tumor is not adequately reported in most of the case-control studies, the exposure is not assessed with reasonable validity, and interviewer bias might be present in most of them.

The major trend of the evidence in the published studies is not clearly in favour of the hypothesis. There is no single study published so far according to the state of the art of epidemiological research which gives reasonable, sound evidence.

All studies with positive associations can just as well be explained by change, bias, confounding or misclassification. Such poorly conducted and inconclusive studies cannot be added or pooled to get convincing evidence, as has been attempted in serious efforts to evaluate the situation [16]. Science should disregard poor studies. False plus false does not equal true.

Going through the eight accepted criteria mentioned in the introduction, only two of them – dose-response relationship and statistical significance – are partly fulfilled if one treats the Hirayama study as conclusive. There is no consistency in the various studies in the sense that the same results are reproduced in similar circumstances. On the contrary the results vary widely. The relative risk increase is small and at best around 2. The exposure and the effect have not been measured with validity and specificity. Bias and confounding factors have not been carefully excluded. There are no intervention studies. The biological plausibility is not convincing. Overall a causal connection cannot be inferred. Applying the IARC levels of evidence, one comes to the conclusion: in-

adequate evidence. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk [23].

Discussion

If passive smoking were an important causal factor for lung cancer, smoking pipes would be a much higher risk for lung cancer than it is. Nonsmoking barkeepers and stewards should have increased lung cancer incidence, which has not been shown. Lung cancer would be much more frequent among nonsmokers – only 5 to 10% of lung cancer cases are nonsmokers. There would also have to be an increase in the incidence of lung cancer in nonsmokers, but this incidence has been rather stable during the last decades [13, 61], as far as we know. There should be histological pre-stages in passive smokers as there are in smokers. This is also not known.

Recent studies [26, 35] have shown that misclassification alone can explain the results of the available case-control studies. Estimating the exposure to passive smoking by cotinine measurements in urine [2, 40, 41] without quality control, and in the way as it has been done in studies so far [42, 58], is not a valid and reliable indicator of exposure of individual cases. A recent evaluation of the evidence on passive smoking [46] could not consider these facts, which were presented at a symposium [45] in October 1986. Whether the presence of many animal carcinogens in sidestream smoke alone – contrasted by missing epidemiological evidence – is a reasonable argument for the assumption that passive smoking causes lung cancer in man, remains an open question.

The toxicological evidence as summarized in [16] is based on exposure data and one the existence of carcinogenic and mutagenic substances in sidestream smoke alone. It is well known that the yield (per cigarette) of several carcinogenic substances and tar is higher in sidestream smoke than in mainstream smoke. The differences are partly due to modern filter techniques. However, analytical measurements of carcinogenic substances in sidestream smoke vary 2 to 10 times, depending on the measuring techniques. The dilution in the air and the physical and chemical processes in the air one or more hours after pollution by sidestream smoke have only recently been investigated [53], showing a fast decay of toxic effects within a short time. To what extent the various carcinogenic substances in sidestream smoke dilute or decay, depending for instance on time length, should be further investigated. Whereas the absorption of nicotine and its pharmacokinetic and metabolism are relatively well known, this does not hold for a single carcinogenic substance contained in sidestream smoke. The amount of absorption of these substances – not the amount inhaled –, how they act on the lung tissue, the metabolic pathways in the body and the way in which they act in man, are not known.

What is known is that there are many carcinogenic substances in sidestream smoke in very small concentrations. The evaluation of this fact depends on the frame of reference. If there is really no threshold for carcinogenic substances – which is the paradigm to which some leading toxicologists presently adhere, but

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which might not be valid for a variety of reasons – and if every risk increase, however small and unlikely it could be, should be avoided, the conclusion must be that passive smoking should be banned from toxicological evidence alone. The first "if" will be answered by toxicology during the next decade and the second "if" should be left to decisions of the society and its institutions and not to toxicologists alone.

We should do all we can to reduce active smoking. Using the argument that epidemiological studies show passive smoking causes lung cancer – if this is not true – might be an obstacle to this goal in the long run. Such a possibly wrong argument might have serious negative effects on the credibility of epidemiology, which should be neither servant of the spirit of the age nor maid of toxicology. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

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